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October 27, 2005

BY FEDERAL EXPRESS

Division of Dockets Management (HFA-305)
U.S. Food and Drug Administration
Room 1061
5630 Fishers Lane
Rockville, MD 20852

Re: **NDA 21-863; Ibuprofen Liquid Filled Gelatin Capsules 200 mg; Ranbaxy Laboratories Ltd.**

CITIZEN PETITION

The undersigned, on behalf of Banner Pharmacaps Inc. of High Point, North Carolina ("Banner") submits this Citizen Petition in quadruplicate pursuant to the Federal Food, Drug and Cosmetic Act ("FDCA"), 21 U.S.C. § 355(b)(2), FDA regulations 21 C.F.R. §§ 10.20, 10.30 and 314.3, FDA's "Guidance for Industry – Applications Covered by Section 505(b)(2)" (October 1999), and FDA's publication *Approved Drug Products with Therapeutic Equivalence Evaluations*, 25th Edition (2005).

I. ACTION REQUESTED

That the Food and Drug Administration ("FDA") refuse to approve the Section 505(b)(2) New Drug Application ("NDA") No. 21-863 filed by Ranbaxy Laboratories Ltd. ("Ranbaxy") seeking regulatory approval for Ibuprofen Liquid Filled Gelatin Capsules 200 mg, on the ground that Ranbaxy's NDA, as amended, fails to include a requisite paragraph III or paragraph IV certification with respect to U.S. Patent No. 6,251,426 owned by Banner and listed in FDA's Orange Book for Banner's listed drug Ibuprofen Liquid Filled Gelatin Capsules 200 mg, in violation of 21 U.S.C. § 355(b)(2)(A) and FDA's related Section 505(b)(2) NDA Guidance.

Ranbaxy evidently expects FDA action on its Section 505(b)(2) NDA for Ibuprofen Liquid Filled Gelatin Capsules on or about November 5, 2005, the one-year PDUFA date for its application. **Banner submits this Citizen Petition requesting FDA to refuse to approve Ranbaxy's NDA due to the absence of a**

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required patent certification.

Ranbaxy must either withdraw its recently-filed amendment and reinstate its paragraph IV certification against the '426 patent, resulting in a delay in final approval of Ranbaxy's NDA until at least 30 months from the date Banner received Ranbaxy's notice of its paragraph IV certification or the ensuing patent litigation brought by Banner against Ranbaxy is resolved, or (b) submit a paragraph III certification that Banner's '426 patent will expire on June 25, 2018, resulting in a delay in final approval of Ranbaxy's NDA until that date.

II. STATEMENT OF GROUNDS

A. Banner's Ibuprofen Listed Drug

Banner is the holder of approved NDA 21-472 for Ibuprofen Liquid Filled Gelatin Capsules 200 mg. Banner's said drug is designated in FDA's publication *Approved Drug Products with Therapeutic Equivalence Evaluations*, 25th Edition (2005)("the Orange Book") as the reference listed drug for Ibuprofen Oral Capsules 200 mg (pertinent Orange Book excerpt attached hereto as Exhibit A). Banner manufactures and sells Ibuprofen Liquid Filled Gelatin Capsules 200 mg pursuant to its approved NDA in interstate commerce.

The Orange Book also lists U.S. Patent No. 6,251,426 ("the '426 patent") for Banner's Ibuprofen Oral Capsules 200 mg (pertinent Orange Book excerpt attached as Exhibit B). The '426 patent (attached Exhibit C) is owned by Banner and claims liquid softgel fill formulations containing ibuprofen in free acid form.

B. Ranbaxy's Ibuprofen Drug Product At Issue

Ranbaxy filed NDA 21-863 for Ibuprofen Liquid Filled Gelatin Capsules 200 mg on or about November 5, 2004 as a Section 505(b)(2) NDA, purporting to rely upon Wyeth's Advil Migraine Liqui-Gels as the sole reference drug product. (Ranbaxy's letter to FDA, May 10, 2005, Exhibit D hereto at 1, 3). As originally filed, Ranbaxy's application contained a paragraph I certification, since there are no patents listed in the Orange Book for Advil Migraine Liqui-Gels. *Id.*

In March 2005, FDA informed Ranbaxy that Ranbaxy was required to amend its application to designate Banner's Ibuprofen Liquid Filled Gelatin Capsules 200 mg as the listed drug, and to include a certification as to Banner's

'426 Orange Book patent. (Exhibit D, at 2). FDA's direction to Ranbaxy was based on the facts that: (a) Ranbaxy's Ibuprofen Liquid Filled Gelatin Capsules 200 mg is composed of the same ibuprofen base (i.e., ibuprofen in free acid form) as Banner's Ibuprofen Liquid Filled Gelatin Capsules 200 mg, (b) Ranbaxy's drug product is pharmaceutically equivalent to Banner's drug product, and (c) Banner's drug product is therefore a listed drug for purposes of Ranbaxy's application. *Id.*

C. Ranbaxy's Patent Certification Amendments

Following FDA's direction, Ranbaxy amended its NDA on March 4, 2005 to include a paragraph IV certification of non-infringement against Banner's '426 patent, and sent notice of this certification to Banner (attached Exhibit E) as required by 21 U.S.C. § 355(j)(2)(B). Banner timely commenced an action for patent infringement against Ranbaxy as authorized by 35 U.S.C. § 271(e) (Exhibit D, at 2), thereby triggering at least a 30-month stay of final approval of Ranbaxy's NDA. 21 U.S.C. § 355(c)(3)(A)(C).

On May 10, 2005, little more than two months after it had filed its paragraph IV certification at FDA's instruction and approximately one month after Banner commenced its patent infringement suit against Ranbaxy, Ranbaxy purported to amend its NDA yet again and withdraw its paragraph IV certification, and so informed FDA (see Exhibit D). More recently, Ranbaxy's counsel wrote to FDA's counsel, claiming that the agency has now changed position and has agreed that no certification is required for the '426 patent (Buc & Beardsley letter of September 20, 2005, attached Exhibit F).[1] While verbal confirmation of FDA's change in position has been provided to Banner's counsel, to Banner's knowledge FDA has made no written statement reversing its original position that a certification as to Banner's '426 patent is required.

Ranbaxy belatedly seeks to avoid the effects of its paragraph IV certification against the '426 patent, namely, Banner's infringement action and the ensuing 30-month stay. Nevertheless, under applicable law, Ranbaxy must make and maintain a paragraph IV certification (or a Paragraph III certification) with respect to Banner's '426 patent, as set forth below.

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[1] Ranbaxy has even gone further, moving on October 17, 2005 to dismiss Banner's patent infringement action, on the ground that no subject matter jurisdiction exists because its paragraph IV certification against the '426 patent has been withdrawn (see Exhibit G attached). Banner intends to oppose Ranbaxy's motion for the reasons set forth in this Citizen Petition, among others.

D. FDA's Interpretation of FDCA Section 505(b)(2) Mandates A Paragraph IV (or III) Certification Against the '426 Patent

1. A Section 505(b)(2) NDA Requires a Certification As To Orange Book Patents Claiming the Listed Drug

A Section 505(b)(2) NDA is an NDA "where at least some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference." "Guidance for Industry – Applications Covered by Section 505(b)(2)", October 1999) ("505(b)(2) Guidance," attached Exhibit H hereto, at 1).[2] *See also* 21 U.S.C. §355(b)(2)(A). A Section 505(b)(2) NDA is typically filed for a drug which is in some respect changed from a previously approved drug product, e.g., a change in dosage form, strength, route of administration, dosing regimen, indication. (505(b)(2) Guidance, Exhibit H, at 4-5).

Regarding patent certification in a Section 505(b)(2) NDA, the governing statute, 21 U.S.C. § 355(b)(2)(A), provides in pertinent part:

> An application submitted under paragraph (1) for a drug for which the investigations described in clause (A) of such paragraph and relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted shall also include—
>
> (A) a certification, in the opinion of the applicant and the best of his knowledge, with respect to each patent which claims the drug for which such investigations were conducted or which claims a use for such drug for which the applicant is seeking approval under this subsection and for which information is required to be filed under paragraph 1 of subsection (c) –
>
> (i) that such patent information has not been filed,
> (ii) that such patent has expired,
> (iii) the date on which the patent will expire, or
> (iv) that such patent is invalid or will not be infringed

[2] While the 505(b)(2) Guidance was issued as a draft guidance in 1999, FDA has been enforcing its provisions since that date, thereby treating it as a controlling guidance.

> (v) by the manufacture, use or sale of the new drug for which the application is submitted...

In its 505(b)(2) Guidance, FDA has interpreted this statutory language, stating that a Section 505(b)(2) NDA must contain:

> "A patent certification or statement as required under Section 505(b)(2) of the Act with respect to any relevant *patents that claim* ***the listed drug*** *and that claim any other drugs on which the investigations relied on for the approval of the application were conducted*, or that claim a use for the listed or other drug."

505(b)(2) Guidance, Exhibit H, at 8 (emphasis supplied).

Therefore, a Section 505(b)(2) applicant must make a certification as to all patents listed in the Orange Book claiming **the listed drug** (as well as against all patents that claim any other drug upon which investigations are relied upon for approval).

In situations where the listed drug is also the drug for which studies relied on by the applicant were conducted, a certification need only be made against Orange Book patents claiming that drug. On the other hand, the Section 505(b)(2) applicant cannot choose to avoid certifying as to patents claiming the listed drug, even where the applicant contends that it is relying upon studies conducted on a drug product other than the listed drug. The Section 505(b)(2) Guidance commands a certification with respect to patents claiming the listed drug, no matter what other drug or studies the applicant claims to rely on (see related discussion at pp. 7-9, *infra*).

2. As the Previously-Approved Pharmaceutical Equivalent, Banner's Ibuprofen Liquid Filled Gelatin Capsules 200 mg Is the Listed Drug

For purposes of a Section 505(b)(2) NDA, a drug is deemed to be a "listed drug" if it satisfies two criteria:

(i) the drug is "a new drug product that has an effective approval under section 505(c) of the act for safety and effectiveness" (21 C.F.R. §314.3), i.e., **a previously approved drug product**; and

(ii) the drug is **the pharmaceutical equivalent** of the drug proposed for approval in the Section 505(b)(2) application.

FDA's Section 505(b)(2) Guidance articulates these criteria as follows:

> "If the 505(b)(2) seeks to rely on the Agency's *previous finding of safety or efficacy for a listed drug or drugs,* identification of any and all listed drugs by established name, proprietary name (if any), dosage form, strength, route of administration, name of the listed drug's sponsor, and the application number...*If there is a listed drug that is the **pharmaceutical equivalent** to the drug proposed in the 505(b)(2) application, **that drug should be identified as the listed drug.**"

505(b)(2) Guidance, Exhibit H, at 7-8 (emphasis supplied).

Drug products are considered "pharmaceutically equivalent" if they have **"the same active ingredient, dosage form, route of administration, and are identical in strength or concentration."** (Orange Book, Preface, at vii, pertinent excerpt in attached Exhibit I).

Here, Banner's Ibuprofen Liquid Filled Gelatin Capsules 200 mg. is the listed drug for Ranbaxy's ibuprofen drug product at issue. This is so because Banner's said drug product is a previously-approved drug product, and is pharmaceutically equivalent to Ranbaxy's proposed drug product. Such pharmaceutical equivalence is evidenced by the facts that:

- Both Ranbaxy's and Banner's drug products have the same active ingredient (ibuprofen base, i.e., ibuprofen in free acid form),
- Both Ranbaxy's and Banner's drug products have the same dosage form (liquid filled gelatin capsule),
- Both Ranbaxy's and Banner's drug products have the same route of administration (oral), and
- Both Ranbaxy's and Banner's drug products have the same strength or concentration (200 mg of such ibuprofen per capsule).

The nexus to patent certification, discussed at pp. 4-5, *supra*, is crystal clear. The Section 505(b)(2) Guidance unequivocally provides that a Section 505(b)(2) applicant must make a certification as to Orange Book patents claiming

the pharmaceutical equivalent drug that is the listed drug:

> "If there is a listed drug that is ***the pharmaceutical equivalent*** of the drug proposed in the 505(b)(2) application, ***the 505(b)(2) applicant should provide patent certifications for the patents listed for the for the pharmaceutically equivalent drug.***"

505(b)(2) Guidance, Exhibit H, at 8 (emphasis supplied).

Quoting this part of the Section 505(b)(2) Guidance, FDA affirmed this principle in a ruling concerning the drug fenofibrate:

> "FDA's Draft Guidance for Industry, Applications Covered by Section 505(b)(2) (Draft Guidance) makes clear, however, that *"[i]f there is a listed drug that is the pharmaceutical equivalent of the drug proposed in the 505(b)(2) application, the 505(b)(2) applicant should provide patent certifications for the patents listed for the pharmaceutically equivalent drug."* ***These provisions ensure that the 505(b)(2) applicant does not use the 505(b)(2) process to end-run patent protections that would have applied had an ANDA been permitted.*** They further ensure that the 505(b)(2) applicant (and FDA) can rely, to the maximum extent possible, on what is already known about a drug without having to re-prove (or re-review) what has already been demonstrated."

FDA Ruling, Docket No. 2004P-0386, Nov. 30, 2004, at 9 (Exhibit I attached) (emphasis supplied).

These precepts are squarely applicable here. Banner's Ibuprofen Liquid Filled Gelatin Capsules is **the pharmaceutical equivalent** of Ranbaxy's proposed drug product, as such is **the listed drug**, and **certifications must be provided** by Ranbaxy as to the '426 patent claiming Banner's pharmaceutically equivalent drug. **Ranbaxy cannot use the Section 505(b)(2) process to end-run patent protections that would have applied had Ranbaxy filed an Abbreviated New Drug Application ("ANDA").**[3]

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[3] Indeed, Ranbaxy's submission could have been filed as an ANDA, which requires identity of active ingredient, dosage form, dosage strength and route of administration. 21 U.S.C. §355(j) (2)(A). While Ranbaxy may contend it had to use the 505(b)(2) vehicle because it seeks a different migraine indication, the basic indication for its product and

Notably, Wyeth's Advil Liqui-Gels relied on by Ranbaxy is **not** a pharmaceutical equivalent of Ranbaxy's ibuprofen product because Advil Liqui-Gels contain a different active ingredient, as Ranbaxy itself admits. In this regard, Ranbaxy stated to FDA:

> "Advil Migraine Liqui-Gels, 200 mg contain solubilized ibuprofen equal to 200 mg ibuprofen as free base and potassium salt. *Ranbaxy's Ibuprofen Liquid Filled Capsules constitute a switch from the approved ibuprofen base and potassium salt to the base form, i.e., active moiety, ibuprofen."*

(Exhibit D, Ranbaxy letter to FDA, May 10, 2005, at 1) (emphasis supplied).[4]

With this "switch" from Wyeth's Advil Liqui-Gels -- ibuprofen base (i.e., ibuprofen in free acid form) in Ranbaxy's product vs. ibuprofen base and potassium salt in the Wyeth product) -- Ranbaxy supposedly justified filing its application as a Section 505(b)(2) NDA.[5] Significantly, however, this change by Ranbaxy from the Advil formulation **underscores** Ranbaxy's need to rely on the true pharmaceutical equivalent -- Banner's listed drug.

Accordingly, FDA's original stance was correct. Without question, Ranbaxy is required to make a certification with respect to the '426 patent, which is listed in the Orange Book for the pharmaceutically equivalent listed drug, Banner's Ibuprofen Liquid Filled Gelatin Capsules 200 mg.

Banner's product is the same – both are pain relievers. If an ANDA had been filed, Banner's drug product would clearly have been the reference listed drug, since it is so listed in the Orange Book, and Ranbaxy would have had to certify as to the '426 patent.

[4] In addition, Ranbaxy acknowledged to Banner in its Paragraph IV notice letter that Ranbaxy's capsules contain ibuprofen base (i.e., ibuprofen in free acid form), the active ingredient in the '426 patent claims: "Ranbaxy's proposed drug products are in the form of liquid-filled gelatin capsules that contain 200 mg of ibuprofen as the active ingredients...These independent claims [of the '426 patent] are as follows: 1. A liquid softgel formulation consisting essentially of : a) greater than 30% by weight ibuprofen in free acid form in solution... All of the claims are directed to formulations of ibuprofen-containing compositions." (Exhibit E, at 1-3).

[5] This was not a change in the chemical form of the active ingredient (e.g., salt or ester) as permitted by the Section 505(b)(2) Guidance (see Exhibit H, at 5), but the elimination of a salt that was used in combination with the active ingredient.

Ranbaxy may also rely upon data in the previously approved NDA for Wyeth's Advil Liqui-Gels (as Banner also did in its approved Section 505(b)(2) NDA). What Ranbaxy cannot do -- as it obviously attempted to do here -- is to avoid Banner's pharmaceutically equivalent listed drug altogether in order to evade having to make a certification as to the '426 patent.

3. Ranbaxy Can Only Make a Paragraph IV (or III) Certification

The '426 patent is issued, listed in the Orange Book and unexpired. Therefore, Ranbaxy's only choices are: (i) to reinstate and maintain the paragraph IV certification it made against Banner's 426 patent on March 4, 2005, requiring Ranbaxy to continue to litigate Banner's infringement action and continued application of the 30-month stay of final approval of Ranbaxy's Section 505(b)(2) NDA, or (ii) to make a paragraph III certification that the patent will expire in June 2018, in which case Ranbaxy's application cannot be approved until that date.

E. Ranbaxy's Apparent Argument to FDA is Unavailing

Ranbaxy apparently argued to FDA that it does not have to certify against the '426 patent, because Section 505(b)(2) application only requires a certification with respect to patents claiming a drug for which investigations are relied upon by a Section 505(b)(2) applicant, and Ranbaxy did not rely upon investigations for Banner's Ibuprofen Liquid Filled Gelatin Capsules (Ranbaxy letter to FDA, May 10, 2005, Exhibit D at 3-4; Ranbaxy letter to FDA, September 20, 2005, Exhibit F, at 1-2).

This contention is without merit. FDA, as the expert Federal agency charged by Congress with interpreting the FDCA, has interpreted 21 U.S.C. § 355(b)(2)(A) as requiring a Section 505(b)(2) applicant to make a patent certification for all Orange Book patents for the pharmaceutically equivalent listed drug, even if the applicant is relying on data for another drug (see pp. 5-8, *supra*). FDA's statutory interpretation is not only correct, but is entitled to substantial deference. *Chevron U.S.A. v. Natural Resources Defense Council,* 467 U.S. 837 (1984).

Ranbaxy's approach would also undermine the uniformity which FDA's interpretation brings to the statutory scheme: each 505(b)(2) applicant is always mandated to make a certification with respect to patents claiming the pharmaceutically equivalent listed drug.

C. ENVIRONMENTAL IMPACT

Petitioner claims a categorical exclusion from the requirement of an environmental assessment or environmental impact statement pursuant to 21 C.F.R. § 25.31.

D. ECONOMIC IMPACT

Pursuant to 21 C.F.R. § 10.30(b), economic impact information is to be submitted only when requested by the Commissioner following review of this Petition.

E. CERTIFICATION

The undersigned certifies that, to their best knowledge and belief, this Citizen Petition includes all information and views upon which the Petition relies, and includes representative data and information known to Petitioner which are unfavorable to the Petition.

Respectfully submitted,

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